REMARKS

A check for the requisite fee for a three month extension of time and additional claims accompanies this response. Any fees that may be due in connection with this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

A DECLARATION under 37 C.F.R. §1.132 has been prepared and will be submitted upon receipt.

Claims 26-29, 31, 32, 35-38, 40, 42, 44-46, 48-54, 57 and 65-87 are presently pending in this application. Claims 25, 30, 33, 39, 43, 47, 55, 56, 58-64 are cancelled herein without prejudice or disclaimer. The subject matter of cancelled claims, such as claim 29 and claim 39, will be pursued in divisional/continuation applications. Applicant reserves the right to file divisional applications to the withdrawn and non-elected subject matter. It is noted that a divisional application U.S. application Serial No. 09/453,851, claiming the subject matter of claims 1-24 and 41 was filed on filed December 2, 1999.

Claims 26-29, 31, 36, 38, 40, 42, 44, 48, 49, 51-53 and 57 are amended. The amendments are designed to more particularly point out and distinctly claim the subject matter that Applicant regards as the invention, and to correct for minor typographical error. The amendments are not designed to avoid art nor to alter the scope of the claims.

Claims 65-87 which recite specific receptors and chemokines and the method for inhibiting activated cells, are added, and find particular basis in the specification as originally filed, including, for example pages 15-27, and elsewhere in the specification.

THE OBJECTIONS TO THE SPECIFICATION AND CLAIMS

The specification and claims are objected to for minor informalities and typographical errors. The typographical and grammatical errors have been corrected herein. The objections to the figure descriptions are being reviewed; amendments thereto will be submitted under separate cover.

THE REJECTION OF CLAIMS 29, 40, 43-45, 53,55, 56 AND 63 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 29, 40, 43-45, 53, 55, 56 and 63 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention on various grounds. The bases for this rejection are set forth below and discussed in turn. Reconsideration of the grounds for rejection is respectfully requested in view of the following remarks and amendments of the claims.

Relevant law

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

There are no requirements for terms to be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, an applicant is entitled to be its own lexicographer [see, *e.g.*, MPEP 2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification. *In re Hill*,

73 USPQ 482 (CCPA 1947)."]. When applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular subject matter and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. § 112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (*Bendix Corp. v United States*, 600 F.2d 1364, 1369, 220 Ct. Cl. 507, 514, 204 USPQ 617, 621 (1979); See, also, *Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1101).

Response and Analysis

1) Claim 29 is rejected because it is alleged that the phrase "animal mammal" renders the claim indefinite, and that the claim should be amended to recite "animal." The claim has been so-amended.

2) Claim 43 is rejected because it is alleged that the phrase "tissue damage-promoting cells" renders the claim indefinite because it is unclear to what cells this language refers. It is respectfully submitted that the this rejection is inapt with respect to claim 43, which has been cancelled and, which did not recite this language. Claim 40 recites this language. Attention is directed to the full phrase in the claim, which is directed to a "method for treating secondary tissue damage " and recites "secondary tissue damage-

promoting cells", not "tissue damage-promoting cells." The specification, which throughout describes the processes by which secondary tissue damage occurs and the associated disorders, describes in detail what is meant by tissue damage-promoting cells. At pages 52 and 53, the specification outlines the inflammatory response and describes the first wave inflammatory response mediators, which lead to the second wave, which released from activated leukocytes and other chemokine receptor-bearing cells:

> Cytokines and chemokines perpetuate their own production and are released from leukocytes via autocrine and paracrine mechanisms. They also induce the synthesis and release of a second wave of inflammatory mediators from the cells that they target. This second wave of inflammatory mediators includes, but are not limited to, neurotoxins, proteolytic enzymes, cationic proteins, arachidonic acid metabolites, and reactive oxygen species. Cytokines and chemokines also induce the expression of cell adhesion molecules and cell surface antigens on leukocytes, endothelial cells, and glial cells, and both events are integral components of the inflammatory response.

In the following pages, the specification describes exemplary disorders and associated secondary tissue damage. Exemplary thereof, is spinal cord injury. At pages 54-57, the specification states:

> Studies on SCI and generalized CNS trauma have demonstrated a clear onset of secondary tissue damage that is observed within a matter of hours, may proceed for several weeks, and is followed by a period of partial recovery. Secondary damage is detectable as cell death, astrogliosis, which leads to glial scarring, neovascularization, demyelination, and loss of sensory and motor function (i.e. paralysis). The time course of secondary damage and partial recovery are well correlated with the degree of inflammation at the site of injury.
>
> The early events in CNS inflammation include activation and proliferation of resident microglia and infiltrating MNPs. Microglia are a distinct class of MNPs and the resident immunoeffector cells of the CNS It is the inflammatory activities of these cells that cause secondary damage at the cellular level. Furthermore, MNP-derived cytokines and chemokines aid in the activation and recruitment of monocytes, neutrophils and T-lymphocytes to the site of injury, a process that is initiated as a consequence of the upregulation of cell surface antigens and cell-adhesion molecules, including integrins, selectins and intercellular

adhesion molecule-1 (I-CAM), on leukocyte subtypes, endothelial cells, and astrocytes. Neutrophils and T-cells contribute to secondary damage by releasing their own cytokines, chemokines, reactive oxygen species, and proteinases into the inflammatory milieu. These inflammatory events lead to the focal death of neurons and oligodendrocytes (the myelin producing cells of the CNS) combined with demyelination of surrounding axons.

Role Of Cytokines In Secondary Damage Of The CNS

MNPs, neutrophils, T-lymphocytes, and astrocytes produce, secrete, and respond to several cytokines including; IL-1, TNF-α, IL-3, IL-4,IL-6, IL-8 GM-CSF, and IFN. These cytokines modulate most leukocyte functions including; phagocytotic activity, the expression of cell surface antigens and cell-adhesion molecules, and the production of oxygen radicals. Furthermore, these cytokines can be directly linked to the glial scarring process, or in some instance, linked via the induced release of neurotoxic and cytotoxic factors. TNF-α has been implicated in the pathogenesis of EAE and several other demyelinating diseases. For example, MNP-specific upregulation of TNF-α, and TNF-α receptors, has been demonstrated in the nervous system of AIDS patients. *In vitro* studies demonstrate that TNF-α is directly cytotoxic to oligodendrocytes and stimulates microglial phagocytosis of myelin. In addition, TNF-α, potentiates the IFN-γ-induced cell death of oligodendrocyte progenitor cells.

Leukocytic and astroglial GM-CSF and IL3, together with T-lymphocytic IL-4, are potent mitogens and activators of MNPs. These factors, along with others, contribute to the pathogenesis of inflammatory autoimmune diseases, most likely by way of the more rapid phagocytosis of myelin discussed earlier In several interesting studies, transgenic mice were designed to produce chronically low levels of either IL-3, IL-6 or TNF-α in the CNS, which led to the proliferation and activation of MNPs in CNS white matter, and subsequently, to primary demyelination and motor disease.

Role Of Chemokines In Secondary Damage Of The CNS

Chemokines, as noted above, are a superfamily of small (approximately about 6 to about 14 kDa), inducible and secreted, chemoattractant cytokines that act primarily on leukocyte subtypes. . . . The receptor binding profiles for a selected exemplary non-limiting group of α and β chemokines is presented in Table 1. Notwithstanding the presence of appropriate receptors, the cell specificity of a given chemokine is largely, although not exclusively, a matter of whether it

> targets MNPs, or neutrophils, or both. In addition, eosinophils are prominent targets for the beta chemokines (see Table 1).
>
> In general, the binding affinities, specificities, and the differential distribution of receptor subtypes across target cells determines the contribution that a given chemokine will make to the inflammatory process. . . .
>
> Chemokines act in an autocrine or paracrine manner and their receptors are upregulated in disease. *In vitro* studies have shown that various stimuli including; lipopolysaccharide (LPS), IL-1, IFN, and TNF-α induce the expression and secretion of chemokines from various CNS and non-CNS cell types. For example, MCP-1, macrophage inflammatory protein-1 beta (MIP-1β) and RANTES (Regulated on Activation, Normal T cell Expressed and Secreted) from astrocytes, microglia, and leukocytes. Once released chemokines concomitantly chemoattract and activate microglia, macrophages, neutrophils, and T-lymphocytes to the site of injury. Chemokine-mediated activation means the induced synthesis and secretion of reactive oxygen species, proteases, and cytokines from the appropriate target cells, with a subsequent increase in secondary damage that is directly attributable to the secreted agents.

At page 61, the specification states:

> Secondary damage of the CNS is exemplary of the progression of events and role of chemokines and chemokine-receptor bearing cells in the progressive damage observed from pathophysiological inflammatory responses. As described below and known to those of skilled in the art, immune effector cells play a role in the pathology of numerous disorders and inflammatory processes, including but not limited to, lung inflammatory disorder, cancers, particularly in solid tumors in which large quantities of infiltrating leukocytes are observed, angiogenesis, viral and bacterial infections, including HIV infection, autoimmune disorders, and others.

The term "secondary tissue damage-promoting cells" refers to host cells, not to invading organisms. As described in the specification, the host cells are mainly of leukocytic lineage but also includes other cell types that secrete inflammatory mediators, such as macrophages, microglia, monocytes (MNPs), neutrophils, eosinophils, basophils, T-lymphocytes, including cytotoxic T-cells, T-helper cells and natural killer cells, B-lymphocytes, mast cells, dendritic cells and (b) astrocytes (glial cells), epithelial cells, endothelial cells, fibroblasts, synoviocytes and cancer cells, and contribute to diseases. All of the cells share

the common property of expressing or upregulating particular chemokine receptors when activated, migrating or proliferating.

Hence, it is clear from the specification that secondary tissue damage-promoting cells include chemokine receptor-bearing cells, such as activated mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, eosiniphils, T lymphocytes and B lymphocytes. Thus, one skilled in the art would understand the language the claims when read in light of the specification. Therefore the claim is not indefinite.

3) Further, it is asserted that claims 43 and 55 indefinite because the metes and bounds of the phrase "a portion thereof" is not known. Cancellation of claims 43 and 55 herein renders these grounds for rejection moot. It is noted, however, with respect to recitation of "a portion" or "a fragment", claims reciting such language further recite that the fragment or portion is effective to facilitate or effect internalization of the conjugate or targeted agent, thereby clearly functionally defining the metes and bounds of "a portion."

4) Claims 44, 45, and 46 are alleged to be confusing because the phrase "plurality of" may refer to different "types" of targeted/targeting agents, or literally, two or more "molecules" of one type of agent. Further, this confusion is allegedly compounded by recitation of the phrase "where the agents are the same." The phrase "plurality" as noted by the Examiner is intended to refer to different types and to two or more of the same type. Hence the phrase is clear.

In claims where there is more than one targeted agent or targeting agent n the conjugate, the targeted agents or targeting agents may all be the same or they may be different from each other. Thus, there may be different "types" of targeted agents or targeting agents, contained in a conjugate and/or, the plurality of targeted agents or targeting agents, contained in a conjugate, may all be of the same "type."

5) Claims 53 and 63 are allegedly confusing because the phrase "targeting agent" is repeated where, in one instance, the phrase should recite "targeted agent" instead of "targeting agent." The inadvertent typographical error in claim 53 is corrected herein to recite "targeted agent." Claim 63 is cancelled herein.

Claims 26, 28, 30-34, 37, 44-52, 56, 57, and 59-64 are rejected because it is asserted that they depend from rejected base claims. Where the rejections of the base claims are overcome, rejection of the claims depending therefrom will be overcome.

THE REJECTION OF CLAIMS 25-38, 40 AND 43-64 UNDER 35 USC § 112, FIRST PARAGRAPH

Claims 25-38, 40, and 43-64 are rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter that is not described in the specification because it is urged:

1) that the specification provides no guidance of how to treat "every possible disorder associated with an inflammatory response";

2) it is not predictable to one of skill in the art how to use a method of treating a patient with "any" type of inflammatory response, because it is urged that Applicants do not give exact dosages or a treatment regimen; and

3) "it is not understood how Applicants can treat a disorder of the immune system of a patient by modulation activation, proliferation and/or migration of inhibited [sic] immune cells without causing other problems.

4) The Examiner also urges that claim 40, which recites "tissue damaging cells" is broader than the enabling disclosure;

5) claims 43 and 55 are allegedly not described in the specification because they recite "a portion thereof"; and

6) claims 53 and 66 are allegedly not described in the specification because of the inadvertent typographical error, correct herein, by reciting targeting agent rather than target*ed* agent.

This rejection is respectfully traversed with respect to 1)-5), and reconsideration of the grounds for this rejection with respect to 6) is respectfully requested in view of the amendments herein that correct the typographical errors.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

1) It is urged that the specification provides no guidance of how to treat "every possible disorder associated with an inflammatory response."

First, it is noted that the claims are not directed to treating "every possible disorder associated with an inflammatory response." The claims are directed to methods of inhibiting pathological conditions associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells

Second, the claims are not directed to the treatment of inflammatory disorders, but are directed methods of pathological conditions associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells. Hence, the methods are directed to treating diseases and disorders that have a common

underlying cause, pathophysiological upregulation of cells that participate in pathophysiological immune responses. In particular, cells that are upregulated in such responses the express chemokine receptors. As described in the specification in great detail, chemokines receptors are expressed on certain classes of activated cells and such cells associated with particular disorders. The methods herein exploit the dynamic nature of chemokine receptor distribution and upregulation that is the hallmark of inflammatory conditions.

As noted, 35 U.S.C. §112, first paragraph does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971)(emphasis added). In this instance, since the disorders and conditions share a common underlying cause, the requirements of § 112, first paragraph, have been fulfilled.

Third, notwithstanding the above, there is no requirement that the specification teach how to treat every inflammatory disorder. Rather, the standard is that the specification teaches how to make and use what is claimed, without undue experimentation. Applying the above-noted factors, it would not require undue experimentation to make and use conjugates that contain a chemokine-receptor targeting agent for delivery of a therapeutic targeted agent.

Evaluation of the above Factors

Breadth of the claims

The claims recite that the targeted cells are activated, proliferating or migrating immune cells, and the methods are for inhibiting the activation, proliferation or migration thereof by delivering a toxic or other therapeutic product. Hence the claims are not directed to methods of treatment of inflammatory responses per se, but to treating diseases and secondary tissue

damage by inhibiting cells that are upregulated in such disease or that promote secondary tissue damage.

The specification provides ample guidance and examples for treating a wide variety of diseases that share this common underlying cause

The specification provides a substantial amount of guidance for selecting particular chemokines for treating a particular disease and for effecting treatment thereof. For example, Table 1 sets for a list of representative chemokines associated with pathophysiological inflammatory responses, including secondary tissue damage, the receptor(s) they bind to, and the cell types affected by each in humans. Table 2 summarizes some exemplary chemokine-receptor targeting agents for treatment of selected diseases and conditions; table 3 provides the amino acid sequences of a variety of chemokines; table 5 provides physical properties of a variety of chemokine targeting agents; table 6 and the examples provide a dozen exemplary conjugates.

The specification also provides a detailed description of disease states associated with the inflammatory response and secondary tissue damage treatment of a provides ample guidance for the treatment of specific and classes of inflammatory disorders (see pages 151-160):

> Exemplary disorders and conditions, in addition to spinal cord injury, include stroke, acute lung injury and acute respiratory distress syndrome (ARDS), Alzheimer's disease, Down's syndrome, inflammatory joint disease, HIV encephalitis, growth, neovascularization (angiogenesis) and metastases of several forms of cancer including, brain, breast, and lung cancers, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis and Crohn's disease, proliferative vitreoretinopathy and uveitis.

The specification describes at least five broad classes of disorders, including cancer, pulmonary diseases, viral infections, secondary tissue damage, inflammatory joint diseases and autoimmune disorders, and includes a description of at least 70 diseases that fall in one or more of these categories

and describes how to select a targeting agent therefor and how to treat each diseases.

In addition, those of skill in the art, as evidenced by the large body of literature directed to chemokines, can readily identify and select an appropriate chemokine or set thereof to use based upon the teachings and guidance in the specification, which teaches how to make conjugates and exemplifies how to test them for requisite activities.

The DECLARATION and Examples provide data demonstrating the activity of at least two different conjugates that rely on chemokines (MCP-1 and SDF-1β) that have very different specificity and selectivity profiles, and shows that each is efficacious for a particular type of disorder.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Presence of working examples and predictability

As discussed above, the specification exemplifies quite a few conjugates, specifically demonstrates synthesis of a dozen and provides data evidencing the activity of at least two. The DECLARATION provides addition *in vitro* and *in vivo* data in recognized model systems evidencing the selectivity and specificity of the conjugates. Having demonstrated that several conjugates perform as described and predicted in the specification, there is no reason to believe that other conjugates prepared and used as taught in the specification and in accord with the claims will not have the desired properties.

Conclusion

Therefore, in light of the extensive teachings and examples in the specification, the teaching of various controls for the method and the high level of skill in the art, the application provides ample guidance sufficient to enable the skilled artisan to practice full scope of the claimed methods.

Furthermore, it is unfair and unduly limiting to require applicant to limit the claims to specific diseases, when the application clearly describes broadly applicable methods. To do so is contrary to the public policy upon which the U.S. patent laws are based. If applicant is required to limit the claims to specific diseases, then those of skill in the art could by virtue of the teachings of this application select chemokines and prepare conjugates for treating other diseases that share upregulation of chemokine-receptor expressing cells as a common element, thereby practicing what is disclosed in the application, but avoid infringing such limited claims. To permit that is simply not fair. The instant application teaches a way of treating a whole array of disorders and conditions and, having done places the public in possession of such knowledge. Having provided this disclosure, it permits others to benefit therefrom. Those of skill in the art should not be permitted to practice what is taught in the application, but avoid infringing the claims.

2) It is alleged that it is "not predictable to one of skill in the art how to use a method of treating a patient with 'any' type of inflammatory response", because "Applicants do not give exact dosages or a treatment regimen."

As discussed above, the claim are not directed to methods for treating a patient with "any" type of inflammatory response, but to treating patients with pathophysiological responses that arise from proliferation, activation or migration of immune cells, which immune cells when proliferating or migrating or when they are activating express chemokine receptors or upregulate such receptors not present on quiescent cells. As discussed above, the specification provides ample guidance for treating such conditions.

Furthermore, the specification does provide guidance for formulation and administration of the conjugates. For example at pages 142 *et seq*, the section entitled "Formulation and administration of compositions containing the conjugates" provides substantial guidance for effecting treatment. At page 146, for example, the specification states:

> The therapeutic agents for use in the methods can be administered by any route known to those of skill in the art, such as, but are not limited to, topically, intraarticularly, intracisternally, intraocularly, intraventricularly, intrathecally, intravenously, intramuscularly, intraperitoneally, intradermally, intratracheally, as well as by any combination of any two or more thereof.
>
> The most suitable route for administration will vary depending upon the disease state to be treated, for example the location of the inflammatory condition. Modes of administration include, but are not limited to, topically, locally, intraarticularly, intracisternally, intraocularly, intraventricularly, intrathecally, intravenously, intramuscularly, intratracheally, intraperitoneally, intradermally, and by a combination of any two or more thereof. For example, for treatment of SCI and other CNS inflammatory conditions, local administration, including administration to the CNS fluid or into the brain (e.g., intrathecally, intraventricularly, or intracisternally) provides the advantage that the therapeutic agent can be administered in a high concentration without risk of the complications that may accompany systemic administration of a therapeutic agent. Similarly, for treatment of inflammatory joint diseases, local administration by injection of the therapeutic agent into the inflamed joint (i.e., intraarticularly) may be preferred. As another example, a disease state associated with an inflammatory skin condition may advantageously be treated by topical administration of the therapeutic agent, for example formulated as a cream, gel, or ointment. For treatment of a disease state associated with an inflammatory lung condition, the preferred route for administration of the therapeutic agent may be by inhalation in an aerosol, or intratracheally . . ..

As discussed above, the following section in the application describes at least 70 disorders that can be treated using the conjugates and in accord with the claimed methods.

3) Further, it is alleged that no guidance is provided, or working examples, for use of the claimed compounds in treating patients who have a

disorder of the immune system, and it is not predictable to one of ordinary skill in the art how to treat such disorders without causing further disorders to the altered immune system.

First, it is noted that the methods herein are not designed for treating disorders of the immune system, but for treating disorders whose underlying cause is the pathophysiological inflammatory response that occurs in connection with a variety of disorders. The methods target cells of the immune system involved in other diseases not a disorder of the immune system. The specification lists more than seventy such disorders, and describes, among other spinal cord injury, which is representative and exemplary, in detail. As stated on described on pages 152 *et seq.*:

> It has been found herein that the cell biology of more than seventy diseases and conditions, involving most organ systems, involved pathophysiological inflammatory responses in a manner similar to the cell biology of acute SCI. The following, non-exhaustive list, and the more detailed treatment of four clinical areas, are designed to illustrate some of the more important similarities. Exemplary disorders and conditions, in addition to spinal cord injury, include stroke, acute lung injury and acute respiratory distress syndrome (ARDS), Alzheimer's disease, Down's syndrome, inflammatory joint disease, HIV encephalitis, growth, neovascularization (angiogenesis) and metastases of several forms of cancer including, brain, breast, and lung cancers, multiple sclerosis, spongiform encephalopathies, sepsis, ulcerative colitis and Crohn's disease, proliferative vitreoretinopathy and uveitis.

As described in the specification and in the DECLARATION, chemokine receptors are upregulated on cells, such as various leukocyte subtypes, that participate in such responses. Hence, the eradication or inhibition of such pathophysiologically upregulated cells should not cause further damage to the immune system. As described, the chemokines and chemokine receptors constitute a large family, so that the chemokine can be selected based upon the cell and particular receptor specifically expressed on the cell. The specification provides exemplary lists of chemokines and identifies the cells upon which they

are regulated and the disorders for which the chemokines could be used as targeting agents.

As described in the specification, and supported by the data in the DECLARATION, targeting delivery of toxins to chemokine-bearing cells provides a means for specific targeted delivery of toxins. The *in vitro* data and *in vivo* xenograft mouse model data shows that the conjugates are specifically targeted to activated cells and do not interact with quiescent cells.

Furthermore, the *in vivo* data presented evidences the relatively low toxicity of the conjugates. The data provided in the DECLARATION shows that even high doses of OPL98111 do not completely eradicate primary human monocytes in culture, since not all of them are in the activated state. Also, a massive (non-therapeutic dose) IP dose (5 mg/kg) of OPL98111 had no apparent effect on the health of mice that were not sacrificed until over 3 weeks after treatment. Throughout the forty days of the course of experiment, mice receiving multiple doses of OPL98111 in two xenograft experiments exhibited no difference in health when compared to placebo treated mice.

4) Claim 40 is rejected as allegedly encompassing subject matter not described in the specification, *i.e.*, a method of treating secondary tissue damage by inhibiting tissue damage-promoting cells. Specifically, such a method allegedly not described because "bacteria and fungi can be considered tissue damage-promoting cells, since they cause damage during infection."

As discussed above with respect to 35 U.S.C. §112, second paragraph, the claim, recites "secondary tissue damage-promoting cells" (as amended, the claim recites "secondary tissue damage-promoting inflammatory cells"). Bacterial and fungi cannot be considered secondary tissue damage-promoting cells. Secondary tissue damage refers to the damage the is caused by pathophysiological inflammatory response that occurs in a variety of disease states and conditions.

In the claimed methods and as described in detail in the specification, secondary tissue damage is treated by inhibiting immune effector cells, including secondary tissue damage-promoting cells, particularly activated leukocytes (or cells activated in a selected disorder) via the chemokine receptors and non-chemokine cytokine receptors expressed by these cells. Neither bacteria nor fungi express cytokine or chemokine receptors; in fact certain pathogens express chemokine receptor-binding proteins and use the chemokine receptors for entry into cells. The instant conjugates can be used to inhibit such entry. At page 15, lines 18 to 22, the description provides that:

> Chemokine receptors constitute a family of receptors that are expressed on activated cells of the leukocyte lineage. ... It is these cells that are targeted herein.

Page 15, lines 25 to 28, page 24, lines 24 to 29, and page 67, Table 1 of the specification, describe such activated cells, including for example activated mononuclear phagocytes, activated leukocytes, activated natural killer cells, activated dendritic cells, and activated T and B lymphocytes. In view of the description, bacteria and fungi clearly are not the secondary tissue damage-promoting cells to which the conjugates are targeted.

5) In addition, claims 43 and 55 are alleged to contain subject matter not described in the specification. In particular, the claims recite "a portion thereof," and the specification provides no guidance or working examples of how a portion of a "target agent and/or a targeted agent" can bind to a cell having the target receptor and be internalized by the cell, or how such a portion can treat an inflammatory response disorder associated with an immune effector cell. The Examiner asserts that it is not predictable to one of skill in the art what portions of the recited agents are required to perform the claimed method, because the function of a peptide cannot be determined based solely on its amino acid sequence.

The claims recite that portion is for specific binding and internalization of linked targeted agents. In view of the specification it would not require undue

experimentation to identify portions of a chemokine or chemokine receptor-targeting agent that would achieve the desired result.

As discussed above, the factors to be considered include, the quantify of experimentation required, the level of skill in the art, the knowledge of those of skill in the art, the guidance in the specification, presence of working examples predictability and breadth of the claims. In this instance, there is a substantial amount of guidance provided in the specification, which teaches and exemplifies assays, cytotoxicity and cell based binding assays, to use to test the conjugates and criteria to use for selecting them. One of skill in the art could readily systematically delete portions of a selected cytokine to identify the minimal or requisite portion of a chemokine or other such agent that would effectively bind to a receptor on a cell by assessing binding and effect internalization by assessing cytotoxicity or looking for internalization of a linked label. As previously noted, the level of skill in this art is recognized to be high and the knowledge of those of skill in the art is extensive, as evidenced by the body of literature, much of it cited in the specification, regarding the identifies, specificities, properties and sequences of chemokines and other chemokine-receptor targeting agents. I think that "those skilled in the art can make good judgments as to which modifications may alter binding capacities, especially since sites necessary for receptor interaction are published and known to those of skill in the art. Furthermore, from a practical standpoint, only active portions of either moiety will be selected for drug manufacture. Truncation and modification of the targeting agent or targeted agent are routinely performed in this art.

For truncated targeted agents see, *e.g.*:

Volk *et al.* cited by the Examiner; Volk *et al.* only uses a truncated PE toxin);

the exemplified targeted is a portion of a portion of a parent compound, the conjugates contain residues 23-268 of the shiga A1 subunit;

Ontak® from Ligand Pharmaceuticals contains a portion/fragment of Diphtheria toxin (Met1-Thr387) (see, also Williams *et al.* (1990) *J Biol Chem* 265:11885-11889).

For truncated targeting agents see, *e.g.*:

A modified (circularly permuted) form of IL-4 is used in chimeras that have increased activity over the wild type and is also fused to a truncated form of PE toxin (Krietman*et al.* (1994) *Proc. Natl. Acad. Sci. U.S.A. 91*:6889-93; Puri*et al.* (1996) *Cancer Res* 56:5631-37 (both moieties truncated);

A biologically active chimera has been successfully synthesized by using a mutant FGF-2 with Cys96 replaced by Ser ([S96]FGF-2) and a recombinant saporin mutant containing a single Cys at the -1 position (Buechler *et al.* (1995) *Eur. J. Biochem* 234:706-13 both moieties);

Several biologically active forms of chemokines with single amino acid substitutions have een reported including RANTES (International PCT application No.WO 98/13495), MIP-1α and MIP-1β (Hunter *et al.* (1995) *Blood* 86:4400-8; Czaplewski, *et al.* (1999) *J. Biol. Chem. 274*:16077-84). There is no reason to believe that there receptor binding capacities would be compromised if a toxin were conjugated to the chemokine C-terminus. N-and C-terminal truncated chemokines (natural or artifact) have been reported that have favorable alterations in their biological activity (*e.g.*, Weber *et al.* (1996) *J. Exp. Med.* 183:681-5; Struyf,*et al.* (1998) *J. Immunol.* 161:2672-5; Wuyts, *et al.* (1999) *Eur. J. Biochem 260*: 421-9; Wuyts, *et al.* (1999) *J. Immunol.* 163:6155-63). Therefore, contrary the assertion of the Examiner, it would be routine to make truncated targeted and targeting agents that result in conjugates that bind to targeted receptors and internalize the linked targeting agents.

Thus, it would be unfair and unduly limiting to require applicant to exclude from the claims portions of chemokine-receptor targeting agents that permit binding and facilitate internalization, when those of skill in the art could readily do so. If the claims are so limited, those of skill in the art could avoid

infringement merely by making routine modifications of the chemokine targeting agents, thereby using the instant disclosure but avoiding infringement.

6) Claims 53 and 63 are alleged to contain subject matter that is not described in the specification, because these claims recite linking a targeting agent with a "targeting agent" and not a "targeted agent." The typographical error is corrected herein, thereby obviating this ground for rejection.

7) Claims 44-54 and 56-64 are rejected because they depend from base claims 43 or 55. Where the rejections of base claims 43 and 55 are overcome then, consequently, this rejection of the claims depending therefrom will be overcome.

THE REJECTION OF CLAIMS 25-38, 40 and 42-64 UNDER 35 U.S.C. §102(b)

Claims 25-38, 40 and 42-64 are rejected under 35 U.S.C. §102(b) as being anticipated by Volk *et al.* because Volk *et al.* discloses a method of treatment of inflammatory responses using a conjugate of a non-chemokine cytokine (IL-2) and a targeted agent (PE40), which is internalized and is associated with the activation of immune effector cells such as T- and B-lymphocytes, and also alleged where the inflammatory response results in secondary tissue damage. It is also urged that Volk *et al.* discloses the inhibition of immune effector cells. This rejection is respectfully traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each

and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The claims

The claims are directed to methods for inhibiting activation, proliferation or migration of immune cells, and/or for treating disorders associated therewith by contacting the immune cells with a conjugate that contains a chemokine-receptor targeting agent and a targeted agent or biologically active portion thereof.

Differences between the claims and the disclosure of the cited reference

Volk *et al.* discloses use of a conjugate of a cytokine IL-2, not a chemokine, with a toxin as an immunosuppressive agent, not as an anti-inflammatory agent. The cytokine is targeted to IL-2 receptor-bearing T-cells, and was shown to inhibit cell-mediated immune responses for use in preventing allograft rejection and autoimmune diseasess.

Volk *et al.* does not disclose the use of a chemokine receptor targeting agent; Il-2 receptors are not chemokine receptors, nor the use of a conjugate of any sort to inhibit migration, proliferation or activation of cells of that express chemokine receptors. Therefore, since Volk *et al.* fails to teach each element as claimed, Volk *et al.* does not anticipate any of the claims.

THE REJECTION OF CLAIMS 25-38, 40 and 42-64 UNDER 35 U.S.C. §103(a)

Claims 25-38, 40, 42-64 are rejected as being unpatentable over the reference of Ogata *et al.* (1989), in view of Volk *et al.* (1994) because Ogata *et al.* teaches the production of a targeting agent (cytokine-IL4) linked to a targeted agent (toxin), but does not teach the use of this conjugate in treating disorders.

It is urged that Volk *et al.* teaches a method of treating an inflammatory response using a conjugate comprising a chemokine [*sic*] targeting agent and a targeted agent (IL2-PE40). The Examiner concludes that, since various cytokines are involved in the modulation of the inflammatory response by stimulating and/or inhibiting immune effector cells, and that "fusion conjugates" using non-chemokine cytokines are useful to treat inflammatory disorders, then it would have been obvious to one of ordinary skill in the art to use the conjugate of Ogata *et al.* in the method of Volk *et al.* This rejection is respectfully traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L.

Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. In re Sernaker, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. In re Papesh, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

The claims

The claim are discussed above.

Differences between the teachings of the cited references and claimed subject matter

Ogata *et al.*

Ogata *et al.* teaches the construction of a recombinant chimeric toxin containing the non-chemokine cytokine, IL-4 linked to the cell binding domain of *Pseudomonas* exotoxin as a reagent for studying the function of the IL-4/Il-4 receptor system. Ogata *et al.* does not teach the use of its conjugate for treatment of any disorders nor suggest substitution of the non-chemokine cytokine with a chemokine.

Page 19, lines 24 to 26, of the description in the instant specification specifically provides that "these [targeting] agents do not include non-chemokine cytokines, such as IL-4...."

Volk *et al.*

Volk teaches that the chimeric protein IL-2-PE40 has been shown to have immunosuppressive efficacy in some models, but has apparently dichotomous effects on humoral and responses. Volk *et al.* appears to resolve this apparent dichotomy by showing that Il-2-PE4- can induce signal transduction in activated T cells before exerting its cytotoxic effect. Since the humoral response requires T cell help for only a limited period, the short-term stimulation of T helper cells by Il-2-PE40 may be sufficient to mediate a B cell response. As a result, the conjugates of Volk *et al.* are not very useful as immunosuppressive agents, since they also mediate a B cell response.

At page 2504, first full paragraph, of the cited reference, Volk *et al.* concludes that:

> Addition of a toxic moiety to IL-2R targeting therapy, like IL-2-PE40, seems to improve the immunosuppressive efficacy on the cell-mediated immune response; but does not solve the problem of an undesired humoral immune response. This conclusion could not be predicted from *in vitro* cytotoxicity experiments. Therefore, the application of IL-2-PE40 immunotherapy has limitations: 1) The production of undesired pathogenically relevant Abs cannot be prevented..., and 2) the formation of Abs to the chimera, particularly to the toxin moiety, may interact with the sometimes required long-term or repeated administration of IL-2-PE40. [emphasis added]

Consequently, Volk *et al.* teaches that its conjugates are not useful for their intended purpose as immunosuppressive agents.

Volk *et al.* neither teaches nor suggests substitution of a chemokine receptor in its conjugate nor the conjugate of Ogata *et al.*, nor does Volk *et al.* Further, as mentioned above, in Section 5, Volk *et al.* does not teach a method of treating inflammatory disorders. Specifically, Volk *et al.* teaches away from using the IL2-PE40 conjugate in IL-2-receptor targeting therapy and concludes

that this conjugate has limitations that prevent such use. Thus, the cited references do not suggest or motivate the combination suggested in the Office Action or claimed in the present application.

The combination of teachings of the cited references does not result in any of the instantly claimed methods

Substitution of the conjugate of Ogata *et al.* in the method of Volk *et al.* does not result in the instantly claimed methods. The combination does not result in method that targets cells that express chemokine receptors. As discussed above, neither Ogata *et al.* nor Volk *et al.*, singly or in any combination thereof, teaches or suggests methods involving targeting chemokine receptors using a conjugate containing a chemokine receptor targeting agent, such as a chemokine. Neither reference teaches or suggests substituting a chemokine for the interleukin used in either conjugate.

Therefore, the Examiner has failed to set forth a prima facie case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: _____
Stephanie Seidman
Registration No. 33,779

Attorney Docket No. 25020-601B
Address all correspondence to:
Heller Ehrman White & McAuliffe LLP
4250 Executive Square, 7th Floor
La Jolla, CA 92037
Telephone: 858 450-8400
Facsimile: 858 587-5360
EMAIL: sseidman@HEWM.com